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PCT

NOTIFICATION CONCERNING
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(PCT Administrative Instructions, Section 411)

To:

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Date of mailing *(day/month/year)* 10 August 2006 (10.08.2006)	
Applicant's or agent's file reference 17808PCTAP	IMPORTANT NOTIFICATION
International application No. PCT/US2006/016804	International filing date *(day/month/year)* 02 May 2006 (02.05.2006)
International publication date *(day/month/year)* **Not yet published**	Priority date *(day/month/year)* 06 May 2005 (06.05.2005)
Applicant ALLERGAN, INC. et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

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Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
06 May 2005 (06.05.2005)	60/678,402	US	30 June 2006 (30.06.2006)

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THE UNITED STATES OF AMERICA

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June 19, 2006

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *60/678,402*
FILING DATE: *May 06, 2005*
RELATED PCT APPLICATION NUMBER: *PCT/US06/16804*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US60/678,402*

Certified by

Jon W. Dudas

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
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PROVISIONAL APPLICATION COVER SHEET
This is a request for filing a PROVISIONAL APPLICATION

Docket No. 17808PROV(AP)		Type a plus sign (+) inside this box →	

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
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TITLE OF THE INVENTION (280 characters max)

SUBSTITUTED BETA-LACTAMS

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ENCLOSED APPLICATION PARTS (check all that apply)

[x] Specification:Number of Pages 49 pgs [ ] Small Entity Statement

[ ] Drawing(s) Number of Sheets _____ [ ] Other (specify):

METHOD OF PAYMENT (check one)

[ ] A check of money order is enclosed to cover the Provisional filing fee [x] The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 01-0885	Provisional Filing Fee Amount **$200.00**	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.
[x] No
[ ] Yes, the name of the U.S. Government agency and the Government contract number are:_____

Respectfully submitted,

SIGNATURE Brent A. Johnson Date: / /

TYPED or PRINTED NAME: Brent A. Johnson, Patent Agent REGISTRATION NO. 51,851

[ ] Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FILING ONLY

SEND COMPLETED FORMS TO: MAIL STOP PROVISIONAL PATENT APPLICATIN, COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Provisional Application of

Old

May 6, 2005

For: THERAPEUTIC SUBSTITUTED β-LACTAMS

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Mail Stop: Provisional Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

The enclosed PROVISIONAL APPLICATION includes the following:

1. Transmittal Letter – 1 pg
2. Return/postage paid Postcard
3. Express Mail Certificate No. EL979999475US
4. Specification (49 pages total) which includes 10 Claims and Abstract

Date: May 6, 2005

By: Bonnie Ferguson
Bonnie Ferguson

CERTIFICATE OF EXPRESS MAIL UNDER 37 C.F.R. §1.10

I hereby certify that this Provisional Patent Application and the documents referred to as enclosed herein are being deposited with the United States Postal Service on May 6, 2005 in an envelope as "Express Mail Post Office To Addressee" mailing label number EL979999475US with sufficient postage for Express Mail addressed to Mail Stop Provisional Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Bonnie Ferguson
Name of person mailing paper

Bonnie Ferguson
Signature of person mailing paper

Date: May 6, 2005

SUBSTITUTED BETA-LACTAMS

By Inventor
David W. Old

BACKGROUND

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

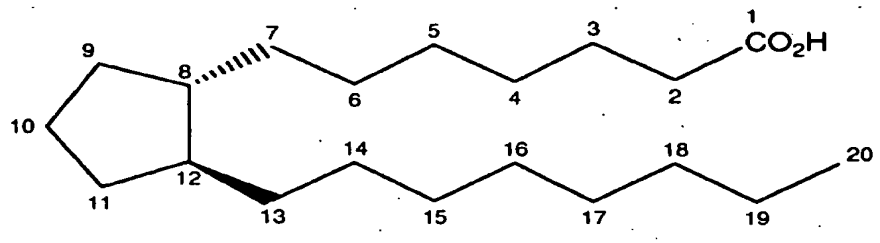
The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupilary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in

iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical β-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Certain eicosanoids and their derivatives are currently commercially available for use in glaucoma management. Eicosanoids and derivatives include numerous biologically important compounds such as prostaglandins and their derivatives. Prostaglandins can be described as derivatives of prostanoic acid which have the following structural formula:



Various types of prostaglandins are known, depending on the structure and substituents carried on the alicyclic ring of the prostanoic acid skeleton. Further classification is based on the number of unsaturated bonds in the side chain indicated by numerical subscripts after the generic type of prostaglandin [e.g. prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2)], and on the configuration of the substituents on the alicyclic ring indicated by α or β [e.g. prostaglandin $F_{2\alpha}$ ($PGF_{2\beta}$)].

Prostaglandin EP_2 selective agonists are believed to have several medical uses. For example, U.S. Patent No. 6,437,146 teaches the use of prostaglandin EP_2 selective agonists "for treating or preventing inflammation and pain in joint and muscle (e.g., rheumatoid arthritis, rheumatoid spondylitis,

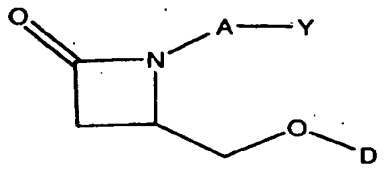
osteoarthritis, gouty arthritis, juvenile arthritis, etc.), inflammatory skin condition (e.g., sunburn, burns, eczema, dermatitis, etc.), inflammatory eye condition (e.g., conjunctivitis, etc.), lung disorder in which inflammation is involved (e.g., asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.), condition of the gastrointestinal tract associated with inflammation (e.g., aphthous ulcer, Chrohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.), gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, allergic disease, systemic lupus crythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjgren's syndrome, Behcet disease, thyroiditis, type I diabetes, diabetic complication (diabetic microangiopathy, diabetic retinopathy, diabetic neohropathy, etc.), nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, kidney dysfunction (nephritis, nephritic syndrome, etc.), liver dysfunction (hepatitis, cirrhosis, etc.), gastrointestinal dysfunction (diarrhea, inflammatory bowel disease, etc.) shock, bone disease characterized by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis), hypercalcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodonritis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculosis, lithiasis (especially, urolithiasis), solid carcinoma, mesangial proliferative glomerulonephritis, edema (e.g. cardiac edema, cerebral edema, etc.), hypertension such as malignant hypertension or the like, premenstrual tension, urinary calculus, oliguria such as the one caused by acute or chronic failure, hyperphosphaturia, or the like."

United State Patent No 6,710,072 teaches the use of EP2 agonists for the treatment or prevention of "osteoporosis, constipation, renal disorders, sexual dysfunction, baldness, diabetes, cancer and in disorder of immune regulation...various pathophysiological diseases including acute myocardial

infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heart failure, and angina pectoris."

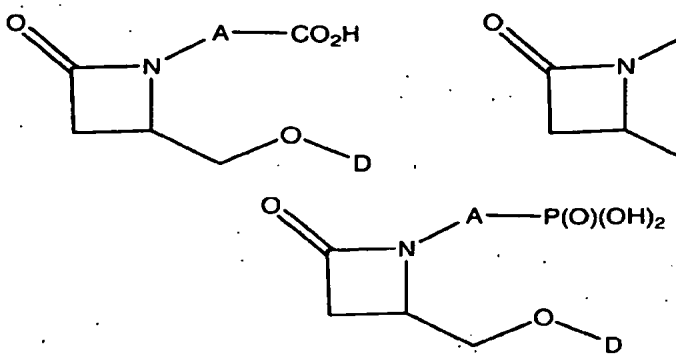
DESCRIPTION OF THE INVENTION

Disclosed herein is a compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group; A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and D is aryl or heteroaryl.

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group. An organic acid functional group is an acidic functional group on an organic molecule. While not intending to be limiting, organic acid functional groups generally comprise an oxide of carbon, sulfur, or phosphorous. Thus, while not intending to limit the scope of the invention in any way, in certain compounds Y is a carboxylic acid, sulfonic acid, or phosphonic acid functional group, i.e. one of the structures shown below.

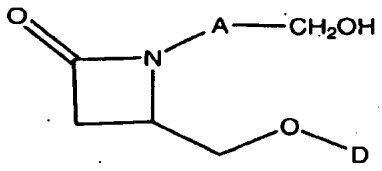


Salts of any of these acids of any pharmaceutically acceptable form are also contemplated.

Additionally, an amide or ester of one of the organic acids shown above comprising up to 12 carbon atoms is also contemplated. In an ester, a hydrocarbyl moiety replaces a hydrogen atom of an acid such as in a carboxylic acid ester, e.g. CO_2Me, CO_2Et, etc.

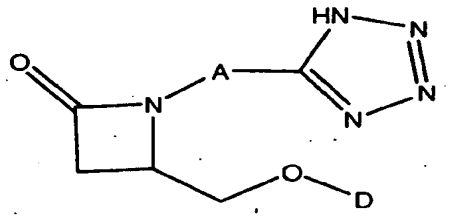
In an amide, an amine group replaces an OH of the acid. Examples of amides include $CON(R^2)_2$, $CON(OR^2)R^2$, $CON(CH_2CH_2OH)_2$, and $CONH(CH_2CH_2OH)$ where R^2 is independently H, C_1-C_6 alkyl, phenyl, or biphenyl. Moieties such as $CONHSO_2R^2$ are also amides of the carboxylic acid notwithstanding the fact that they may also be considered to be amides of the sulfonic acid R^2-SO_3H.

While not intending to limit the scope of the invention in any way, Y may also be hydroxymethyl or an ether thereof comprising up to 12 carbon atoms. Thus, compounds having a structure shown below are possible.

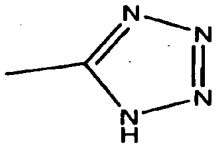


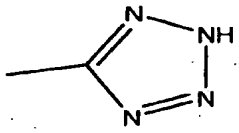
Additionally, ethers of these compounds are also possible. An ether is a functional group wherein a hydrogen of an hydroxyl is replaced by carbon, e.g., Y is CH_2OCH_3, $CH_2OCH_2CH_3$, etc.

Finally, while not intending to limit the scope of the invention in any way, Y may be a tetrazolyl functional group, such as compounds having a structure according to the formula below.

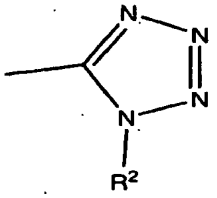


An unsubstituted tetrazolyl functional group has two tautomeric forms, which can rapidly interconvert in aqueous or biological media, and are thus equivalent to one another. These tautomers are shown below.





Additionally, if R^2 is C_1-C_6 alkyl, phenyl, or biphenyl, other isomeric forms of the tetrazolyl functional group such as the one shown below are also possible, all of these are considered to be within the scope of the term "tetrazolyl."



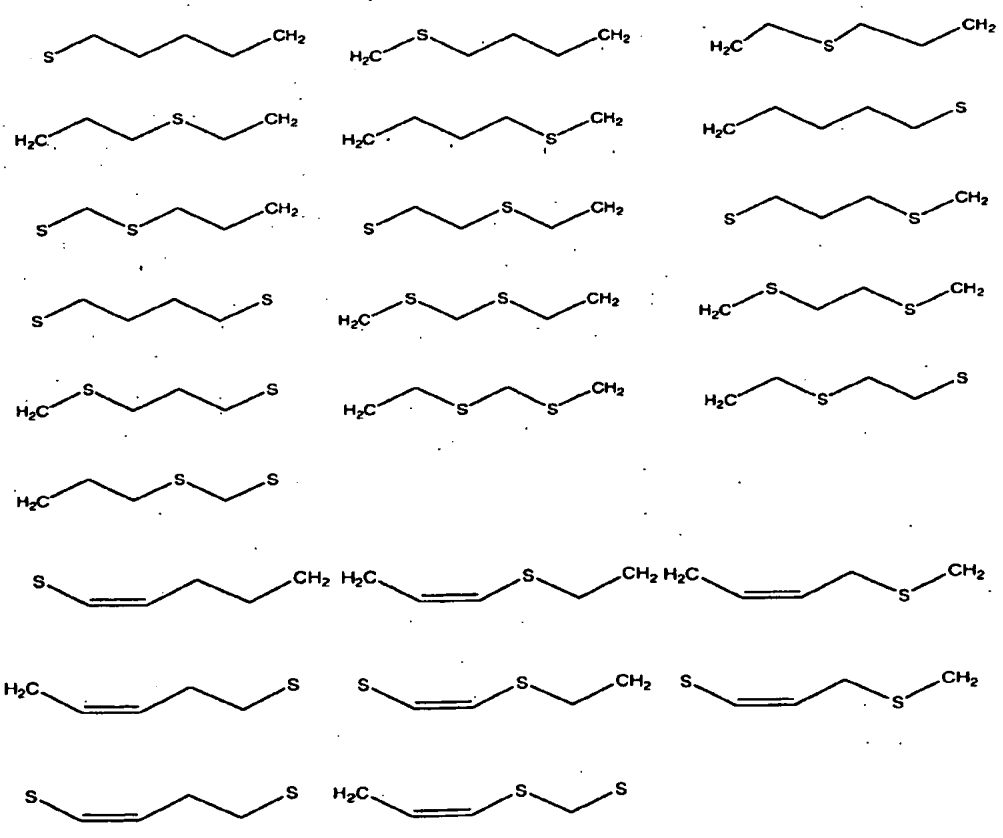
While not intending to limit the scope of the invention in any way, in one embodiment, Y is selected from the group consisting of $CO_2(R^2)$, $CON(R^2)_2$, $CON(OR^2)R^2$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH,

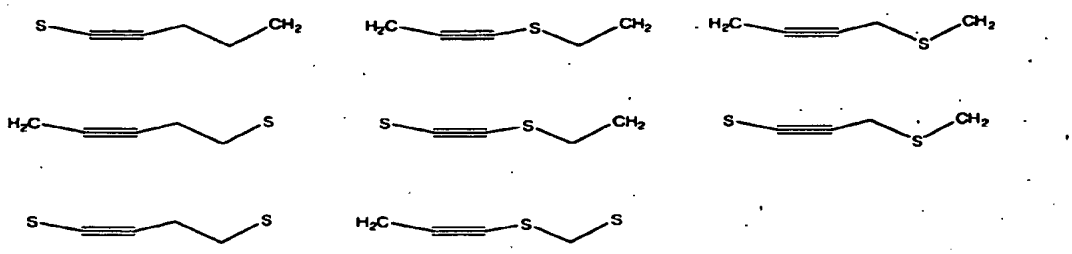
$P(O)(OH)_2$, $CONHSO_2R^2$, $SO_2N(R^2)_2$, SO_2NHR^2, and tetrazolyl-R^2; wherein R^2 is independently H, C_1-C_6 alkyl, phenyl, or biphenyl.

In relation to the identity of A disclosed in the chemical structures presented herein, A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_n-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O.

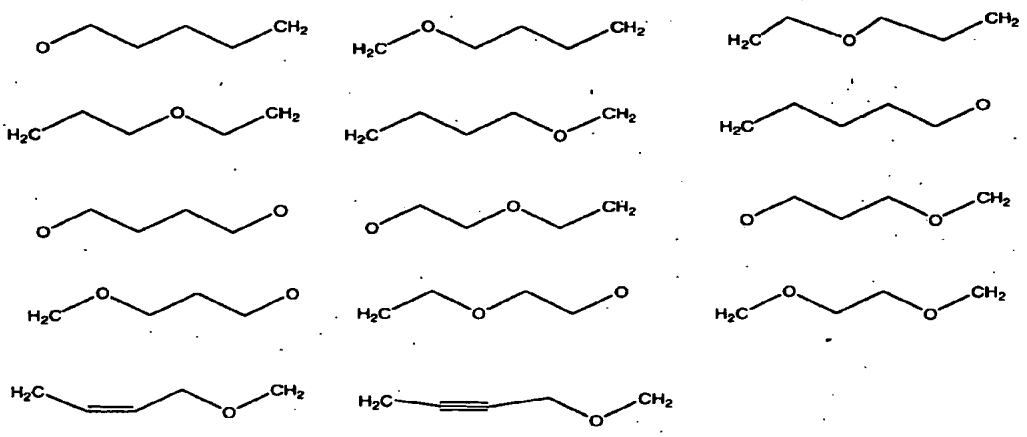
While not intending to be limiting, A may be $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$.

Alternatively, A may be a group which is related to one of these three moieties in that any carbon is substituted with S and/or O. For example, while not intending to limit the scope of the invention in any way, A may be an S substituted moiety such as one of the following or the like.

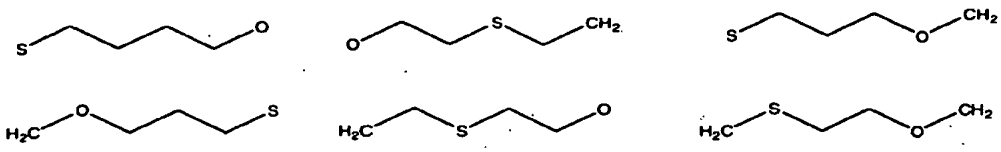




Alternatively, while not intending to limit the scope of the invention in any way, A may be an O substituted moiety such as one of the following or the like.



Alternatively, while not intending to limit the scope of the invention in any way, A may have both an O and an S substituted into the chain, such as one of the following or the like.



Alternatively, while not intending to limit the scope of the invention in any way, in certain embodiments A is $-(CH_2)_n$-Ar-$(CH_2)_o$- wherein Ar is

interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O. In other words, while not intending to limit the scope of the invention in any way,

in one embodiment A comprises from 1 to 4 CH_2 moieties and Ar, e.g. -CH_2-Ar-, -$(CH_2)_2$-Ar-, -CH_2-Ar-CH_2-, -CH_2Ar-$(CH_2)_2$-, -$(CH_2)_2$-Ar-$(CH_2)_2$-, and the like; or

A comprises O, from 0 to 3 CH_2 moieties, and Ar, e.g., -O-Ar-, Ar-CH_2-O-, -O-Ar-$(CH_2)_2$-, -O-CH_2-Ar-, -O-CH_2-Ar-$(CH_2)_2$, and the like; or

A comprises S, from 0 to 3 CH_2 moieties, and Ar, e.g., -S-Ar-, Ar-CH_2-S-, -S-Ar-$(CH_2)_2$-, -S-CH_2-Ar-, -S-CH_2-Ar-$(CH_2)_2$, -$(CH_2)_2$-S-Ar, and the like.

In another embodiment, the sum of n and o is from 2 to 4 wherein one CH_2 may be substituted with S or O.

In another embodiment, the sum of n and o is 3 wherein one CH_2 may be substituted with S or O.

In another embodiment, the sum of n and o is 2 wherein one CH_2 may be substituted with S or O.

In another embodiment, the sum of n and o is 4 wherein one CH_2 may be substituted with S or O.

Interarylene or heterointerarylene refers to an aryl ring or ring system or a heteroaryl ring or ring system which connects two other parts of a molecule, i.e. the two parts are bonded to the ring in two distinct ring positions. Interarylene or heterointerarylene may be substituted or unsubstituted. Unsubstituted interarylene or heterointerarylene has no substituents other than the two parts of the molecule it connects. Substituted interarylene or heterointerarylene has substituents in addition to the two parts of the molecule it connects.

In one embodiment, Ar is substituted or unsubstituted interphenylene, interthienylene, interfurylene, interpyridinylene, interoxazolylene, and interthiazolylene. In another embodiment Ar is interphenylene (Ph). In another embodiment A is –$(CH_2)_2$-Ph-. While not intending to limit scope of the invention in any way, substituents may have 4 or less heavy atoms, or in other

words, non hydrogen atoms. Any number of hydrogen atoms required for a particular substituent will also be included. Thus, the substituent may be hydrocarbyl having up to 4 carbon atoms, including alkyl up to C_4, alkenyl, alkynyl, and the like;

hydrocarbyloxy up to C_3;

CF_3;

halo, such as F, Cl, or Br;

hydroxyl;

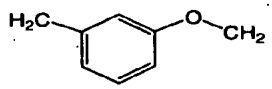
NH_2 and alkylamine functional groups up to C_3;

other N or S containing substituents;

and the like.

In one embodiment A is $-(CH_2)_m$-Ar-$(CH_2)_o$- wherein Ar is interphenylene, the sum of m and o is from 1 to 3, and wherein one CH_2 may be substituted with S or O.

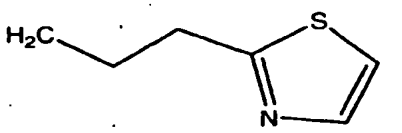
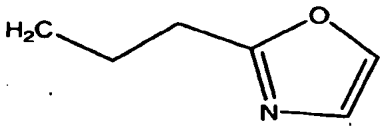
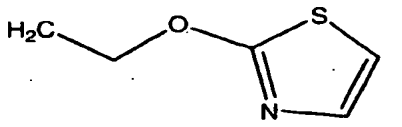
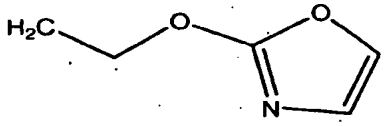
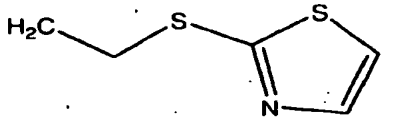
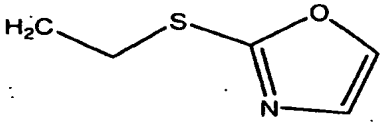
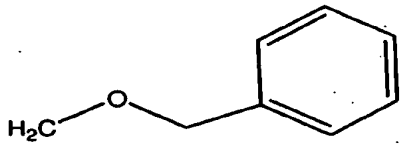
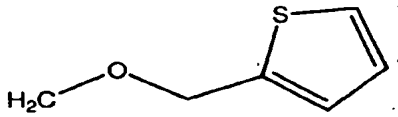
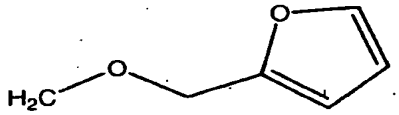
In another embodiment A is -CH_2-Ar-OCH_2-. In another embodiment A is –CH_2-Ar-OCH_2- and Ar is interphenylene. In another embodiment, Ar is attached at the 1 and 3 positions, otherwise known as *m*-interphenylene, such as when A has the structure shown below.



In another embodiment A is $-(CH_2)_6$-, *cis* $-CH_2CH=CH-(CH_2)_3$-, or $-CH_2C\equiv C-(CH_2)_3$-, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_2$-Ph- wherein one CH_2 may be substituted with S or O.

In another embodiment A is $-(CH_2)_6$-, *cis* $-CH_2CH=CH-(CH_2)_3$-, or $-CH_2C\equiv C-(CH_2)_3$-, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_2$-Ph-.

In other embodiments, A has one of the following structures, where Y is attached to the aromatic or heteroaromatic ring.

In another embodiment A is $-CH_2OCH_2Ar$.

In another embodiment A is $-CH_2SCH_2Ar$.

In another embodiment A is $-(CH_2)_3Ar$.

In another embodiment A is $-CH_2O(CH_2)_4$.

In another embodiment A is $-CH_2S(CH_2)_4$.

In another embodiment A is $-(CH_2)_6-$.

In another embodiment A is *cis* $-CH_2CH=CH-(CH_2)_3-$.

In another embodiment A is $-CH_2C\equiv C-(CH_2)_3-$.

In another embodiment A is $-S(CH_2)_3S(CH_2)_2-$.

In another embodiment A is $-(CH_2)_4OCH_2-$.

In another embodiment A is *cis* $-CH_2CH=CH-CH_2OCH_2-$.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene,.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene,.

In another embodiment A is -CH_2-O-$(CH_2)_4$-.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene,.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene,.

D is aryl or heteroaryl.

Aryl is an unsubstituted or substituted aromatic ring or ring system such as phenyl, naphthyl, biphenyl, and the like.

Heteroaryl is aryl having one or more N, O, or S atoms in the ring, i.e. a ring carbon is substituted by N, O, or S. While not intending to be limiting, examples of heteroaryl include unsubstituted or substituted thienyl, pyridinyl, furyl, benzothienyl, benzofuryl, imidizololyl, indolyl, and the like.

The substituents of aryl or heteroaryl may have up to 12 non-hydrogen atoms each and as many hydrogen atoms as necessary. Thus, while not intending to limit the scope of the invention in any way, the substituents may be:

hydrocarbyl, such as alkyl, alkenyl, alkynyl, and the like, including linear, branched or cyclic hydrocarbyl, and combinations thereof;

hydrocarbyloxy, meaning O-hydrocarbyl such as OCH_3, OCH_2CH_3, O-cyclohexyl, etc, up to 11 carbon atoms;

hydroxyhydrocarbyl, meaning hydrocarbyl-OH such as CH_2OH, $C(CH_3)_2OH$, etc, up to 11 carbon atoms;

nitrogen substituents such as NO_2, CN, and the like, including

amino, such as NH_2, $NH(CH_2CH_3OH)$, $NHCH_3$, and the like up to 11 carbon atoms;

carbonyl substituents, such as CO_2H, ester, amide, and the like;

halogen, such as chloro, fluoro, bromo, and the like

fluorocarbyl, such as CF_3, CF_2CF_3, etc.;

phosphorous substituents, such as PO_3^{2-}, and the like;

sulfur substituents, including S-hydrocarbyl, SH, SO_3H, SO_2-hydrocarbyl, SO_3-hydrocarbyl, and the like.

In certain embodiments, the number of non-hydrogen atoms is 6 or less in a substituent. In other embodiments, the number of non-hydrogen atoms is 3 or less in a substituent. In other embodiments, the number of non-hydrogen atoms on a substituent is 1.

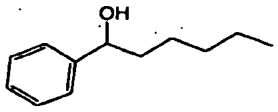
In certain embodiments, the substituents contain only hydrogen, carbon, oxygen, halogen, nitrogen, and sulfur. In other embodiments, the substituents contain only hydrogen, carbon, oxygen, and halogen.

Unless otherwise indicated, references to aryl, heteroaryl, phenyl, thienyl, benzothienyl, and the like are intended to mean both the substituted and the unsubstituted moiety.

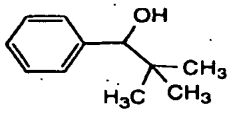
Thus, compounds wherein D is any of the above classes or species of aryl or heteroaryl are contemplated herein.

Further, while not intending to limit the scope of the invention in any way, in one embodiment D is phenyl. In another embodiment D is chlorophenyl, meaning phenyl with one or more chloro substituents. In another embodiment D is 3,5-dichlorophenyl. In another embodiment D is unsubstituted phenyl.

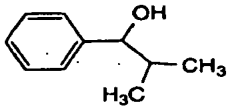
In other useful compounds, D is one of the structures shown below, with the corresponding name of the structures shown.



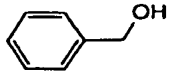
(1-hydroxyhexyl)phenyl



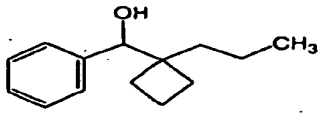
(1-hydroxy-2,2-dimethylpropyl)phenyl



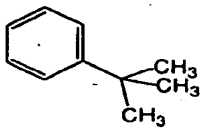
(1-hydroxy-2-methylpropyl)phenyl



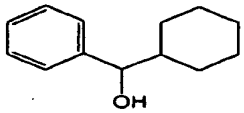
(hydroxymethyl)phenyl



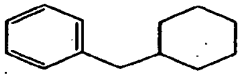
[(1-propylcyclobutyl)hydroxymethyl]phenyl



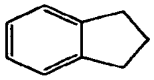
t-butylphenyl



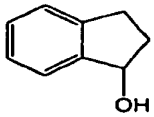
(cyclohexylhydroxymethyl)phenyl



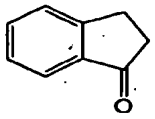
(cyclohexylmethyl)phenyl



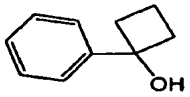
indanyl



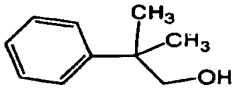
indanolyl



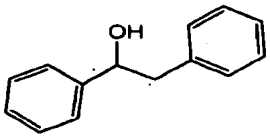
indanonyl



(1-hydroxycyclobutyl)phenyl

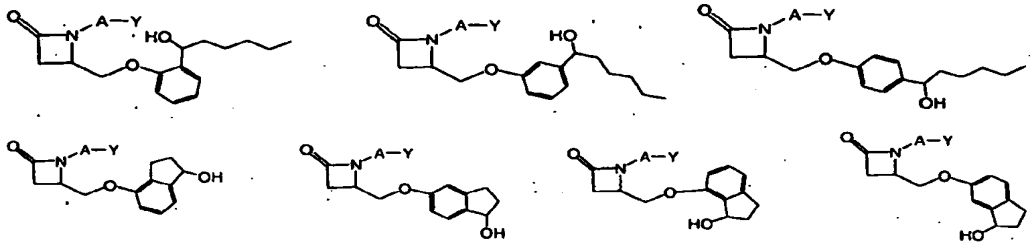


(2-methyl-3-hydroxypropyl)phenyl



(1-hydroxy-2-phenylethyl)phenyl

Attachment to the remaining part of the molecule, i.e. the oxygen of the $-OCH_2-$ connected to the β-lactam occurs at the phenyl ring at any position. For example, the compounds shown below, or pharmaceutically acceptable salts or prodrugs thereof, are contemplated.



In one embodiment D is (1-hydroxyhexyl)phenyl.

In another embodiment D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment D is (hydroxymethyl)phenyl.

In another embodiment D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment D is t-butylphenyl.

In another embodiment D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment D is (cyclohexylmethyl)phenyl.

In another embodiment D is indanyl.

In another embodiment D is indanolyl.

In another embodiment D is indanonyl.

In another embodiment D is (1-hydroxycyclobutyl)phenyl.

In another embodiment D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment D is (1-hydroxy-2-phenylethyl)phenyl.

In one embodiment A is $-(CH_2)_6-$, and D is (1-hydroxyhexyl)phenyl.

In another embodiment A is *cis* $-CH_2CH=CH-(CH_2)_3-$, and D is (1-hydroxyhexyl)phenyl.

In another embodiment A is $-CH_2C{\equiv}C\text{-}(CH_2)_3\text{-}$, and D is (1-hydroxyhexyl)phenyl.

In another embodiment A is $\text{-}S(CH_2)_3S(CH_2)_2\text{-}$, and D is (1-hydroxyhexyl)phenyl.

In another embodiment A is $\text{-}(CH_2)_4OCH_2\text{-}$, and D is (1-hydroxyhexyl)phenyl.

In another embodiment A is *cis* $-CH_2CH{=}CH\text{-}CH_2OCH_2\text{-}$, and D is (1-hydroxyhexyl)phenyl.

In another embodiment A is $-CH_2CH{\equiv}CH\text{-}CH_2OCH_2\text{-}$, and D is (1-hydroxyhexyl)phenyl.

In another embodiment A is $\text{-}(CH_2)_2S(CH_2)_3\text{-}$, and D is (1-hydroxyhexyl)phenyl.

In another embodiment A is $\text{-}CH_2\text{-Ph-}OCH_2\text{-}$, wherein Ph is interphenylene, and D is (1-hydroxyhexyl)phenyl.

In another embodiment A is $\text{-}CH_2\text{-mPh-}OCH_2\text{-}$, wherein mPh is *m*-interphenylene, and D is (1-hydroxyhexyl)phenyl.

In another embodiment A is $\text{-}CH_2\text{-O-}(CH_2)_4\text{-}$, and D is (1-hydroxyhexyl)phenyl.

In another embodiment A is $\text{-}CH_2\text{-O-}CH_2\text{-Ar-}$, wherein Ar is 2,5-interthienylene, and D is (1-hydroxyhexyl)phenyl.

In another embodiment A is $\text{-}CH_2\text{-O-}CH_2\text{-Ar-}$, wherein Ar is 2,5-interfurylene, and D is (1-hydroxyhexyl)phenyl.

In one embodiment A is $-(CH_2)_6\text{-}$, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is *cis* $-CH_2CH{=}CH\text{-}(CH_2)_3\text{-}$, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is $-CH_2C{\equiv}C\text{-}(CH_2)_3\text{-}$, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is $\text{-}S(CH_2)_3S(CH_2)_2\text{-}$, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is -$(CH_2)_4OCH_2$-, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2-, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is –$CH_2CH\equiv CH$-CH_2OCH_2-, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$-, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$-, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and D is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In one embodiment A is –$(CH_2)_6$-, and D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-$(CH_2)_3$-, and D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is –$CH_2C\equiv C$-$(CH_2)_3$-, and D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$-, and D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is -$(CH_2)_4OCH_2$-, and D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2-, and D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$, and D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$, and D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is $-CH_2-Ph-OCH_2-$, wherein Ph is interphenylene, and D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is $-CH_2-mPh-OCH_2-$, wherein mPh is *m*-interphenylene, and D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is $-CH_2-O-(CH_2)_4-$, and D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interthienylene, and D is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interfurylene, and D is (1-hydroxy-2-methylpropyl)phenyl.

In one embodiment A is $-(CH_2)_6-$, and D is (hydroxymethyl)phenyl.

In another embodiment A is *cis* $-CH_2CH=CH-(CH_2)_3-$, and D is (hydroxymethyl)phenyl.

In another embodiment A is $-CH_2C\equiv C-(CH_2)_3-$, and D is (hydroxymethyl)phenyl.

In another embodiment A is $-S(CH_2)_3S(CH_2)_2-$, and D is (hydroxymethyl)phenyl.

In another embodiment A is $-(CH_2)_4OCH_2-$, and D is (hydroxymethyl)phenyl.

In another embodiment A is *cis* $-CH_2CH=CH-CH_2OCH_2-$, and D is (hydroxymethyl)phenyl.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$, and D is (hydroxymethyl)phenyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$, and D is (hydroxymethyl)phenyl.

In another embodiment A is $-CH_2-Ph-OCH_2-$, wherein Ph is interphenylene, and D is (hydroxymethyl)phenyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and D is (hydroxymethyl)phenyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$-, and D is (hydroxymethyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and D is (hydroxymethyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and D is (hydroxymethyl)phenyl.

In one embodiment A is –$(CH_2)_6$-, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is *cis* –CH_2CH=CH-$(CH_2)_3$-, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is –$CH_2C\equiv C$-$(CH_2)_3$-, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$-, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is -$(CH_2)_4OCH_2$-, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2-, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is –$CH_2CH\equiv CH$-CH_2OCH_2-, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$-, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$-, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and D is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In one embodiment A is –$(CH_2)_6$-, and D is t-butylphenyl.

In another embodiment A is *cis* –CH_2CH=CH-$(CH_2)_3$-, and D is t-butylphenyl.

In another embodiment A is –$CH_2C\equiv C$-$(CH_2)_3$-, and D is t-butylphenyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$-, and D is t-butylphenyl.

In another embodiment A is -$(CH_2)_4OCH_2$-, and D is t-butylphenyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2-, and D is t-butylphenyl.

In another embodiment A is –$CH_2CH\equiv CH$-CH_2OCH_2-, and D is t-butylphenyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$-, and D is t-butylphenyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and D is t-butylphenyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and D is t-butylphenyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$-, and D is t-butylphenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and D is t-butylphenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and D is t-butylphenyl.

In one embodiment A is –$(CH_2)_6$-, and D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-$(CH_2)_3$-, and D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is –$CH_2C\equiv C$-$(CH_2)_3$-, and D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is $-S(CH_2)_3S(CH_2)_2-$, and D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is $-(CH_2)_4OCH_2-$, and D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is *cis* $-CH_2CH=CH-CH_2OCH_2-$, and D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$, and D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$, and D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is $-CH_2$-Ph-OCH_2-, wherein Ph is interphenylene, and D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is $-CH_2$-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is $-CH_2-O-(CH_2)_4-$, and D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2$-Ar-, wherein Ar is 2,5-interthienylene, and D is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2$-Ar-, wherein Ar is 2,5-interfurylene, and D is (cyclohexylhydroxymethyl)phenyl.

In one embodiment A is $-(CH_2)_6-$, and D is (cyclohexylmethyl)phenyl.

In another embodiment A is *cis* $-CH_2CH=CH-(CH_2)_3-$, and D is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2C\equiv C-(CH_2)_3-$, and D is (cyclohexylmethyl)phenyl.

In another embodiment A is $-S(CH_2)_3S(CH_2)_2-$, and D is (cyclohexylmethyl)phenyl.

In another embodiment A is $-(CH_2)_4OCH_2-$, and D is (cyclohexylmethyl)phenyl.

In another embodiment A is *cis* $-CH_2CH=CH-CH_2OCH_2-$, and D is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$, and D is (cyclohexylmethyl)phenyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$, and D is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2-Ph-OCH_2-$, wherein Ph is interphenylene, and D is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2-mPh-OCH_2-$, wherein mPh is *m*-interphenylene, and D is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2-O-(CH_2)_4-$, and D is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interthienylene, and D is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interfurylene, and D is (cyclohexylmethyl)phenyl.

In one embodiment A is $-(CH_2)_6-$, and D is indanyl.

In another embodiment A is *cis* $-CH_2CH=CH-(CH_2)_3-$, and D is indanyl.

In another embodiment A is $-CH_2C\equiv C-(CH_2)_3-$, and D is indanyl.

In another embodiment A is $-S(CH_2)_3S(CH_2)_2-$, and D is indanyl.

In another embodiment A is $-(CH_2)_4OCH_2-$, and D is indanyl.

In another embodiment A is *cis* $-CH_2CH=CH-CH_2OCH_2-$, and D is indanyl.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$, and D is indanyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$, and D is indanyl.

In another embodiment A is $-CH_2-Ph-OCH_2-$, wherein Ph is interphenylene, and D is indanyl.

In another embodiment A is $-CH_2-mPh-OCH_2-$, wherein mPh is *m*-interphenylene, and D is indanyl.

In another embodiment A is $-CH_2-O-(CH_2)_4-$, and D is indanyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and D is indanyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and D is indanyl.

In one embodiment A is –$(CH_2)_6$-, and D is indanolyl.

In another embodiment A is *cis* –CH_2CH=CH-$(CH_2)_3$-, and D is indanolyl.

In another embodiment A is –$CH_2C\equiv C$-$(CH_2)_3$-, and D is indanolyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$-, and D is indanolyl.

In another embodiment A is -$(CH_2)_4OCH_2$-, and D is indanolyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2-, and D is indanolyl.

In another embodiment A is –$CH_2CH\equiv CH$-CH_2OCH_2-, and D is indanolyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$-, and D is indanolyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and D is indanolyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and D is indanolyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$-, and D is indanolyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and D is indanolyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and D is indanolyl.

In one embodiment A is –$(CH_2)_6$-, and D is indanonyl.

In another embodiment A is *cis* –CH_2CH=CH-$(CH_2)_3$-, and D is indanonyl.

In another embodiment A is –$CH_2C\equiv C$-$(CH_2)_3$-, and D is indanonyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$-, and D is indanonyl.

In another embodiment A is -$(CH_2)_4OCH_2$-, and D is indanonyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2-, and D is indanonyl.

In another embodiment A is –$CH_2CH{\equiv}CH$-CH_2OCH_2-, and D is indanonyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$-, and D is indanonyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and D is indanonyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and D is indanonyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$-, and D is indanonyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and D is indanonyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and D is indanonyl.

In one embodiment A is –$(CH_2)_6$-, and D is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-$(CH_2)_3$-, and D is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is –$CH_2C{\equiv}C$-$(CH_2)_3$-, and D is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$-, and D is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -$(CH_2)_4OCH_2$-, and D is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2-, and D is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is –$CH_2CH{\equiv}CH$-CH_2OCH_2-, and D is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$-, and D is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and D is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and D is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$-, and D is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and D is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and D is (1-hydroxycyclobutyl)phenyl.

In one embodiment A is –$(CH_2)_6$-, and D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-$(CH_2)_3$-, and D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is –$CH_2C\equiv C$-$(CH_2)_3$-, and D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$-, and D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is -$(CH_2)_4OCH_2$-, and D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2-, and D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is –$CH_2CH\equiv$CH-CH_2OCH_2-, and D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$-, and D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$-, and D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and D is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and D is (2-methyl-3-hydroxypropyl)phenyl.

In one embodiment A is –$(CH_2)_6$-, and D is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-$(CH_2)_3$-, and D is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is –$CH_2C\equiv C$-$(CH_2)_3$-, and D is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$-, and D is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is -$(CH_2)_4OCH_2$-, and D is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2-, and D is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is –$CH_2CH\equiv CH$-CH_2OCH_2-, and D is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$-, and D is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and D is (1-hydroxy-2-phenylethyl)phenyl.

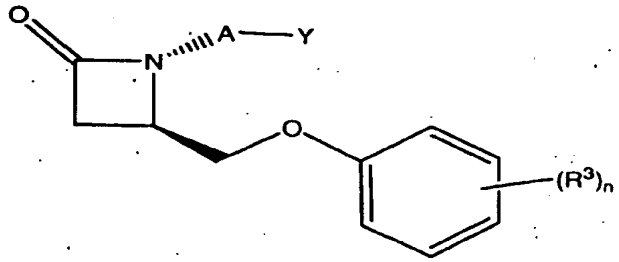
In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and D is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$-, and D is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and D is (1-hydroxy-2-phenylethyl)phenyl.

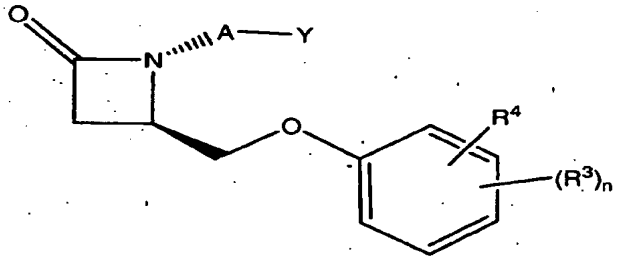
In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interfurylene, and D is (1-hydroxy-2-phenylethyl)phenyl.

One embodiment comprises



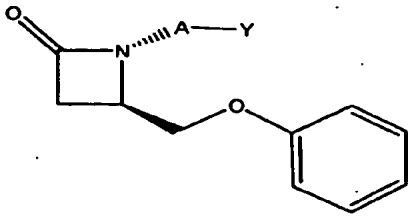
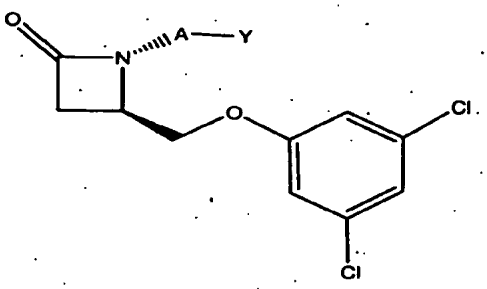
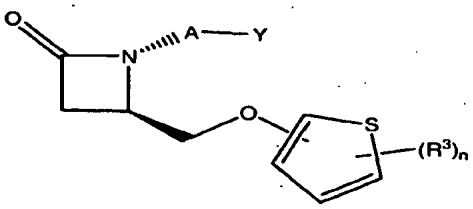
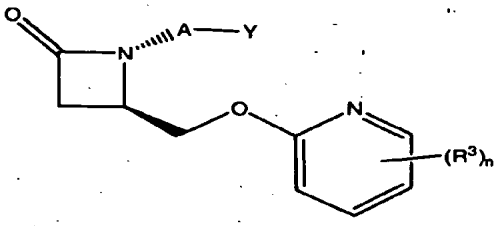
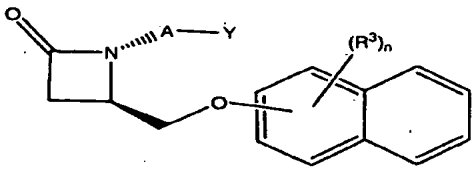
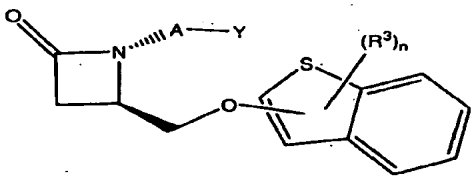
or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof;
R^3 is independently methyl, ethyl, isopropyl, fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, NH_2, OH, CN, NO_2, or CF_3; and
n is 0, 1, 2, or 3.

Another embodiment comprises

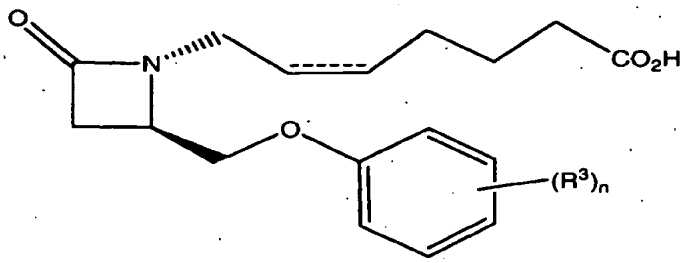


or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof;
wherein A and Y are as described herein;
R^3 is independently methyl, ethyl, isopropyl, fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, NH_2, OH, CN, NO_2, or CF_3;
R^4 is hydroxyhydrocarbyl having from 1 to 10 carbon atoms; and
n is 0, 1, 2, or 3.

Other embodiments comprise compounds according to the structures below, or pharmaceutically acceptable salts or prodrugs thereof. In these embodiments A is as described herein; and
Y, R^3 and n are as described herein.

Another embodiment comprises



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof;

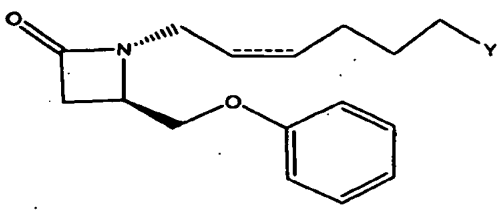
wherein a dashed line indicates the presence or absence of a covalent bond

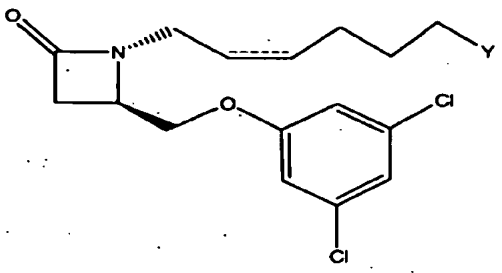
A is as described herein;

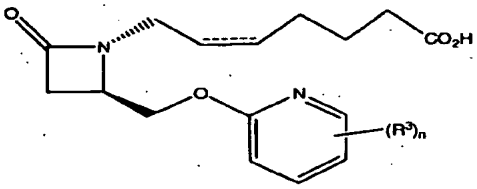
R^3 is independently methyl, ethyl, isopropyl, fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, NH_2, OH, CN, NO_2, or CF_3; and

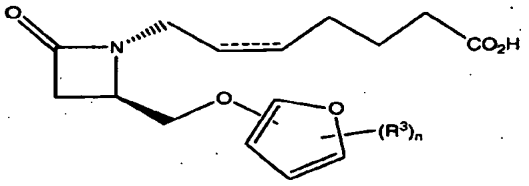
n is 0, 2, or 3.

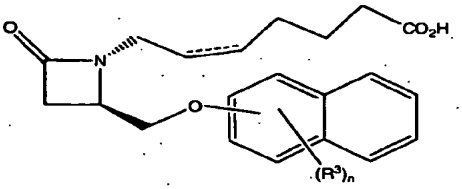
Other embodiments comprise compounds according to the structures below, or pharmaceutically acceptable salts or prodrugs thereof. In these embodiments Y, R^3 and n are as described herein.

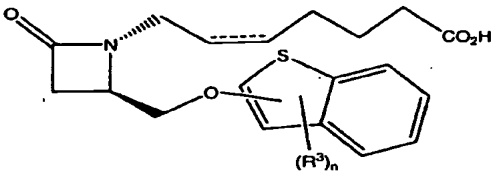


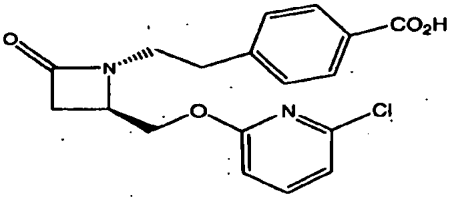


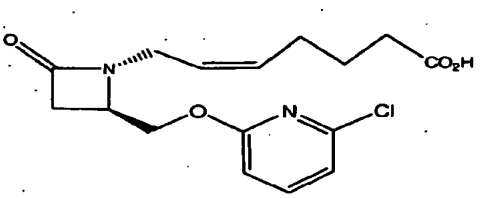


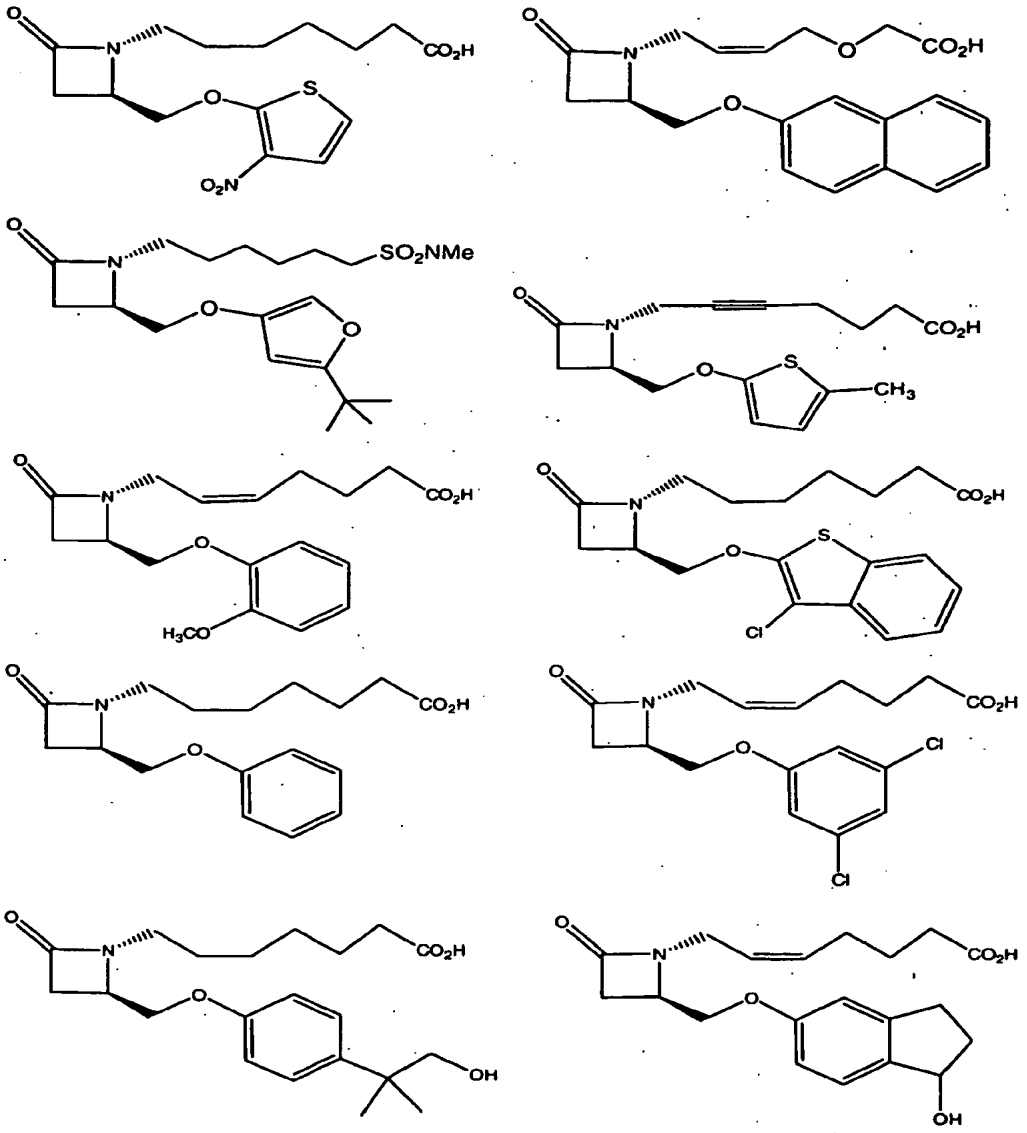












Another embodiment is a compound comprising a 4-(aryloxymethyl)azetidin-2-one or a 4-(heteroaryloxymethyl)azetidin-2-one, substituted at the beta lactam nitrogen with a prostaglandin α chain, wherein said compound is active at a prostaglandin EP2 receptor.

Aryloxymethyl is methyl having attached to an -OAr substituent, where Ar is aryl. Heteroaryloxymethyl is methyl attached to an –OHet substituent,

where Het is heteroaryl. Aryloxy or heteroaryloxy is substituted or unsubstituted, i.e. the aryl or heteroaryl may be substituted or unsubstituted.

A prostaglandin α chain is any moiety which is the α-chain of any known prostaglandin, i.e. an analog for the numbered carbons 1-7 on the prostanoic acid structure shown above.

Pharmaceutically acceptable salts or prodrugs or metabolites of the above listed compounds are also contemplated.

The determination of whether a compound is active at a prostaglandin EP2 receptor is well within the ability of a person of ordinary skill in the art. While not intending to limit the scope of the invention in any way, one method of making such a determination is also provided in the examples herein.

The compounds of disclosed herein are useful for the prevention or treatment of glaucoma or ocular hypertension in mammals, or for the manufacture of a medicament for the treatment of glaucoma or ocular hypertension. They are also useful for the treatment of those diseases disclosed in the art as being amenable to treatment by prostaglandin EP_2 agonist, such as the ones listed previously.

A "pharmaceutically acceptable salt" is any salt that retains the activity of the parent compound and does not impart any additional deleterious or untoward effects on the subject to which it is administered and in the context in which it is administered compared to the parent compound. A pharmaceutically acceptable salt also refers to any salt which may form in vivo as a result of administration of an acid, another salt, or a prodrug which is converted into an acid or salt.

Pharmaceutically acceptable salts of acidic functional groups may be derived from organic or inorganic bases. The salt may comprise a mono or polyvalent ion. Of particular interest are the inorganic ions, lithium, sodium, potassium, calcium, and magnesium. Organic salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Hydrochloric acid or some other pharmaceutically acceptable acid

may form a salt with a compound that includes a basic group, such as an amine or a pyridine ring.

A "prodrug" is a compound which is converted to a therapeutically active compound after administration, and the term should be interpreted as broadly herein as is generally understood in the art. While not intending to limit the scope of the invention, conversion may occur by hydrolysis of an ester group or some other biologically labile group. Generally, but not necessarily, a prodrug is inactive or less active than the therapeutically active compound to which it is converted. Ester prodrugs of the compounds disclosed herein are specifically contemplated. An ester may be derived from a carboxylic acid of C1 (i.e. the terminal carboxylic acid of a natural prostaglandin), or an ester may be derived from a carboxylic acid functional group on another part of the molecule, such as on a phenyl ring. While not intending to be limiting, an ester may be an alkyl ester, an aryl ester, or a heteroaryl ester. The term alkyl has the meaning generally understood by those skilled in the art and refers to linear, branched, or cyclic alkyl moieties. C_{1-6} alkyl esters are particularly useful, where alkyl part of the ester has from 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, pentyl isomers, hexyl isomers, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and combinations thereof having from 1-6 carbon atoms, etc.

A metabolite is broadly defined as a compound which is formed in vivo from the disclosed compound.

Those skilled in the art will readily understand that for administration or the manufacture of medicaments the compounds disclosed herein can be admixed with pharmaceutically acceptable excipients which per se are well known in the art. Specifically, a drug to be administered systemically, it may be confected as a powder, pill, tablet or the like, or as a solution, emulsion, suspension, aerosol, syrup or elixir suitable for oral or parenteral administration or inhalation.

For solid dosage forms or medicaments, non-toxic solid carriers include, but are not limited to, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, the polyalkylene glycols, talcum,

cellulose, glucose, sucrose and magnesium carbonate. The solid dosage forms may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distcarate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release. Liquid pharmaceutically administrable dosage forms can, for example, comprise a solution or suspension of one or more of the presently useful compounds and optional pharmaceutical adjutants in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like. Typical examples of such auxiliary agents are sodium acetate, sorbitan monolaurate, triethanolamine, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 16th Edition, 1980. The composition of the formulation to be administered, in any event, contains a quantity of one or more of the presently useful compounds in an amount effective to provide the desired therapeutic effect.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol and the like. In addition, if desired, the injectable pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like.

The amount of the presently useful compound or compounds administered is, of course, dependent on the therapeutic effect or effects desired, on the specific mammal being treated, on the severity and nature of the mammal's condition, on the manner of administration, on the potency and pharmacodynamics of the particular compound or compounds employed, and on the judgment of the prescribing physician. The therapeutically effective dosage of the presently useful compound or compounds is preferably in the range of about 0.5 or about 1 to about 100 mg/kg/day.

A liquid which is ophthalmically acceptable is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid should either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions should preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride,

mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	1-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The compounds disclosed herein are also useful in combination with other drugs useful for the treatment of glaucoma or other conditions.
For the treatment of glaucoma, combination treatment with the following classes of drugs is contemplated:

β-Blockers (or β-adrenergic antagonists) including carteolol, levobunolol, metiparanolol, timolol hemihydrate, timolol maleate, β1-selective antagonists such as betaxolol, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Adrenergic Agonists including

non-selective adrenergic agonists such as epinephrine borate, epinephrine hydrochloride, and dipivefrin, and the like, or pharmaceutically acceptable salts or prodrugs thereof; and

α_2-selective adrenergic agonists such as apraclonidine, brimonidine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Carbonic Anhydrase Inhibitors including acetazolamide, dichlorphenamide, methazolamide, brinzolamide, dorzolamide, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Cholinergic Agonists including

direct acting cholinergic agonists such as charbachol, pilocarpine hydrochloride, pilocarbine nitrate, pilocarpine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

chlolinesterase inhibitors such as demecarium, echothiophate, physostigmine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

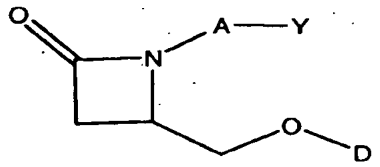
Glutamate Antagonists such as memantine, amantadine, rimantadine, nitroglycerin, dextrophan, detromethorphan, CGS-19755, dihydropyridines, verapamil, emopamil, benzothiazepines, bepridil, diphenylbutylpiperidines, diphenylpiperazines, HOE 166 and related drugs, fluspirilene, eliprodil, ifenprodil, CP-101,606, tibalosine, 2309BT, and 840S, flunarizine, nicardipine, nifedimpine, nimodipine, barnidipine, verapamil, lidoflazine, prenylamine lactate, amiloride, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Prostamides such as bimatoprost, or pharmaceutically acceptable salts or prodrugs thereof; and

Prostaglandins including travoprost, UFO-21, chloprostenol, fluprostenol, 13,14-dihydro-chloprostenol, latanoprost and the like.

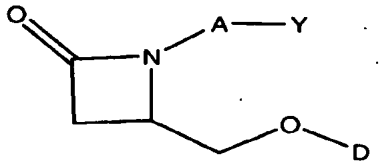
The compounds disclosed herein are selective prostaglandin EP_2 agonists, and are thus useful for the treatment of glaucoma, ocular hypertension, the other diseases or conditions disclosed herein.

One embodiment is a method comprising administering an effective amount of a compound to a mammal for the treatment or prevention of glaucoma or ocular hypertension, said compound comprising



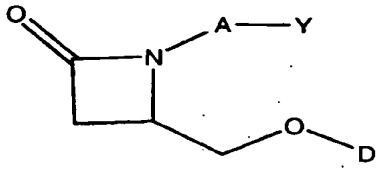
or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof;
wherein Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;
A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$
wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and
D is aryl or heteroaryl.

Another embodiment is a method comprising administering an effective amount of a compound to a mammal for the treatment or prevention of glaucoma or ocular hypertension, said compound comprising



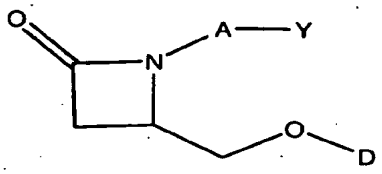
or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein A and Y are as defined above and D is phenyl.

Another embodiment is a method comprising administering an effective amount of a compound to a mammal for the treatment or prevention of glaucoma or ocular hypertension, said compound comprising



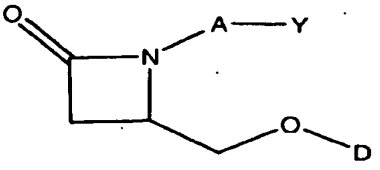
or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein A and Y are as defined above and D is chlorophenyl.

Another embodiment is a method comprising administering an effective amount of a compound to a mammal for the treatment or prevention of glaucoma or ocular hypertension, said compound comprising



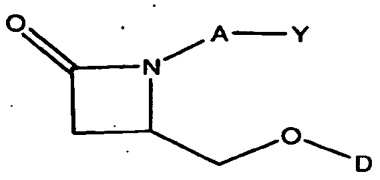
or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein A and Y are as defined above and D is 3,5-dichlorophenyl.

Another embodiment is a method comprising administering an effective amount of a compound to a mammal for the treatment or prevention of glaucoma or ocular hypertension, said compound comprising



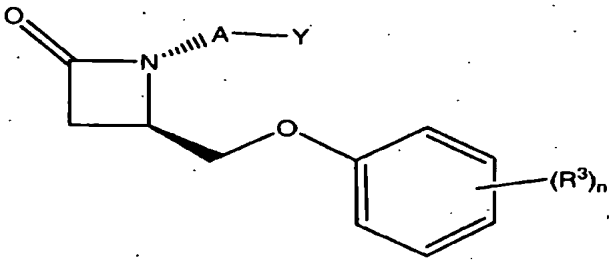
or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein A and Y are as defined above and D is unsubstituted phenyl.

Another embodiment is a method comprising administering an effective amount of a compound to a mammal for the treatment or prevention of glaucoma or ocular hypertension, said compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$ and Y and D are as defined above.

Another embodiment is a method comprising administering an effective amount of a compound to a mammal for the treatment or prevention of glaucoma or ocular hypertension, said compound comprising

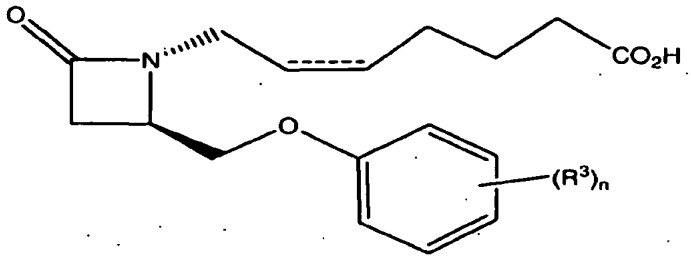


or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein A and Y are as defined above,

R^3 is independently methyl, ethyl, isopropyl, fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, NH_2, OH, CN, NO_2, or CF_3; and

n is 0, 1, 2, or 3.

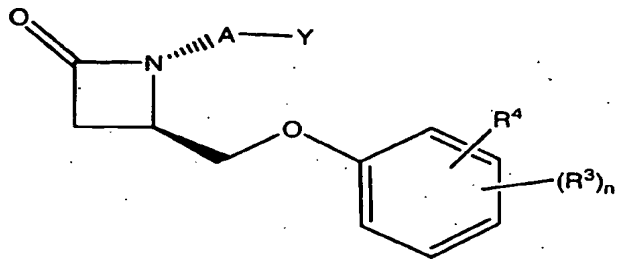
Another embodiment is a method comprising administering an effective amount of a compound to a mammal for the treatment or prevention of glaucoma or ocular hypertension, said compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof;

wherein a dashed line indicates the presence or absence of a covalent bond and R^3 and n are as defined above.

Another embodiment is a method comprising administering an effective amount of a compound to a mammal for the treatment or prevention of glaucoma or ocular hypertension, said compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein A and Y are as defined above;

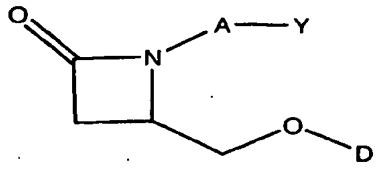
R^3 is independently methyl, ethyl, isopropyl, fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, NH_2, OH, CN, NO_2, or CF_3;

R^4 is hydroxyhydrocarbyl having from 1 to 10 carbon atoms; and

n is 0, 1, 2, or 3.

Another embodiment is a method comprising administering an effective amount of a compound to a mammal for the treatment or prevention of glaucoma or ocular hypertension, said compound comprising a 4-(aryloxymethyl)azetidin-2-one or a 4-(heteroaryloxymethyl)azetidin-2-one, substituted at the beta lactam nitrogen with a prostaglandin α chain, wherein said compound is active at a prostaglandin EP_2 receptor.

One embodiment is a compound comprising

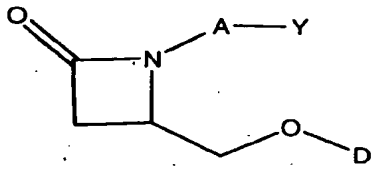


or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and

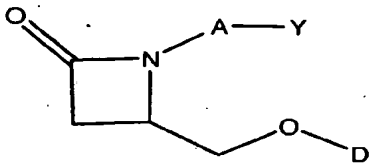
D is aryl or heteroaryl.

Another embodiment is a compound comprising



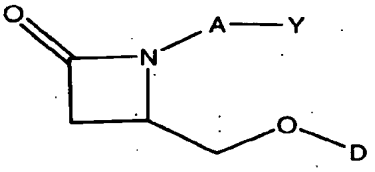
or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein A and Y are as defined above and D is phenyl.

Another embodiment is a compound comprising



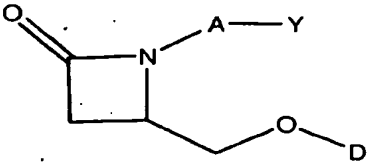
or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein A and Y are as defined above and D is chlorophenyl.

Another embodiment is a compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein A and Y are as defined above and D is 3,5-dichlorophenyl.

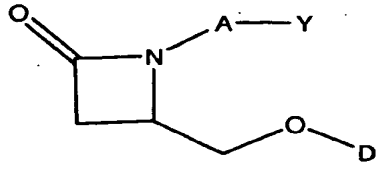
Another embodiment is a compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof;

wherein A and Y are as defined above and D is unsubstituted phenyl.

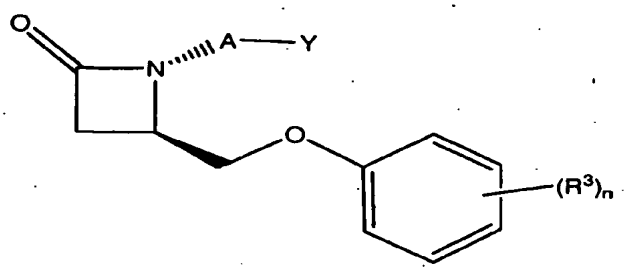
Another embodiment is a compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof;

wherein A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$ and Y and D are as defined above.

Another embodiment is a compound comprising



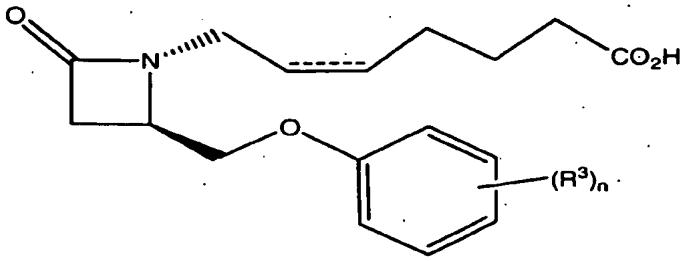
or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof;

wherein A and Y are as defined above,

R^3 is independently methyl, ethyl, isopropyl, fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, NH_2, OH, CN, NO_2, or CF_3; and

n is 0, 1, 2, or 3.

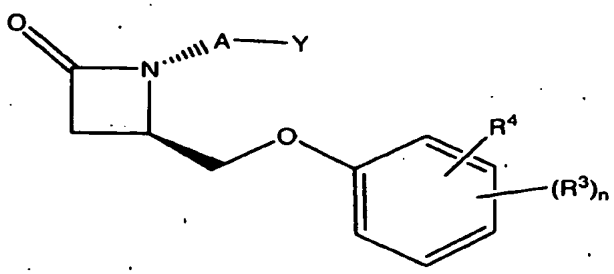
Another embodiment is a compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof;

wherein a dashed line indicates the presence or absence of a covalent bond and R^3 and n are as defined above.

Another embodiment is a compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof;
wherein A and Y are as defined above;
R^3 is independently methyl, ethyl, isopropyl, fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, NH_2, OH, CN, NO_2, or CF_3;
R^4 is hydroxyhydrocarbyl having from 1 to 10 carbon atoms; and
n is 0, 1, 2, or 3.

Another embodiment is a compound comprising a 4-(aryloxymethyl)azetidin-2-one or a 4-(heteroaryloxymethyl)azetidin-2-one, substituted at the beta lactam nitrogen with a prostaglandin α chain, wherein said compound is active at a prostaglandin EP_2 receptor.

Another embodiment comprises administering an effective amount of a compound to a mammal for the treatment or prevention of glaucoma or ocular hypertension, said compound comprising any compound or class of compounds disclosed herein.

Another embodiment comprises administering an effective amount of a compound to a mammal for the treatment or prevention of inflammatory bowel disease, said compound comprising any compound or class of compounds disclosed herein.

Another embodiment comprises a liquid comprising a compound, wherein said liquid is ophthalmically acceptable, said compound comprising any compound or class of compounds disclosed herein.

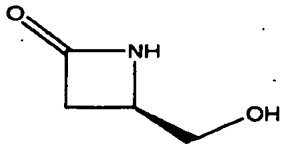
Another embodiment comprises use of a compound in the manufacture of a medicament for the treatment of glaucoma or ocular hypertension in a mammal, said compound comprising any compound or class of compounds disclosed herein.

Another embodiment comprises use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel in a mammal, said compound comprising any compound or class of compounds disclosed herein.

Synthetic Procedures

While there are many methods of preparing the compounds disclosed herein, in one method the compound shown below may be prepared by the procedures described in Chemistry Letters, (2), 293-6; 1987 or United States Patent No. 4,174,316, where the R, α-, or natural amino acid is substituted for the β or S amino acid used in the references.

Alternatively, (4R)-N-(*tert*-butyldimethylsilyl)azetidin-2-one-4-carboxylic acid (commercially available from Acros Chemical Company) could be converted in two steps (reduction [e.g. LiBH4, MeOH] and deprotection [e.g 1 N HCl, MeOH] to the compound shown below.



The α-chain may be added by adapting procedures known in the art, such as those described in U.S. Patent Application Publication No. 20030207925, U.S. Patent Application Publication No. 20030120079, and U.S. Patent No. 6,747,054.

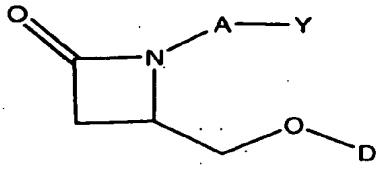
The ω-chain may be constructed by procedures known in the art, such as those described in U.S. Patent Application Serial No. 60/644,069 filed on January 14, 2005.

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

CLAIMS

What is claimed is:

1. Use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel disease, said compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof;
wherein Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;
A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and
D is aryl or heteroaryl.

2. Use of claim 1 wherein D in said compound is phenyl.

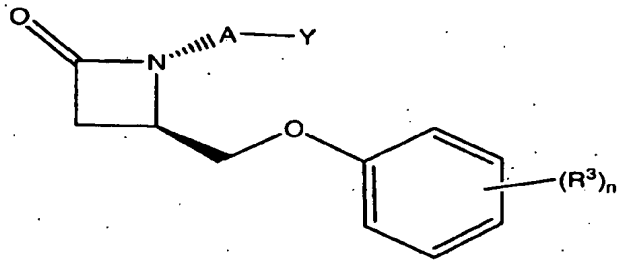
3. Use of claim 2 wherein D in said compound is chlorophenyl.

4. Use of claim 3 wherein D in said compound is 3,5-dichlorophenyl.

5. Use of claim 2 wherein D in said compound is unsubstituted phenyl.

6. Use of claim 1 wherein A in said compound is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$.

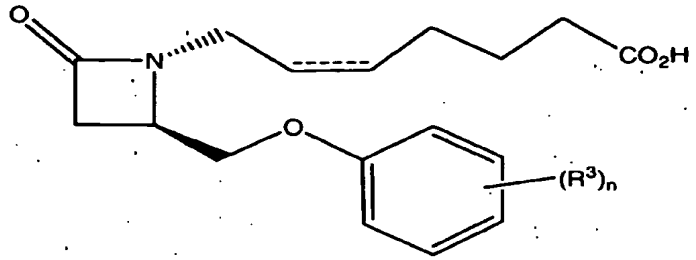
7. Use of claim 2, said compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof;

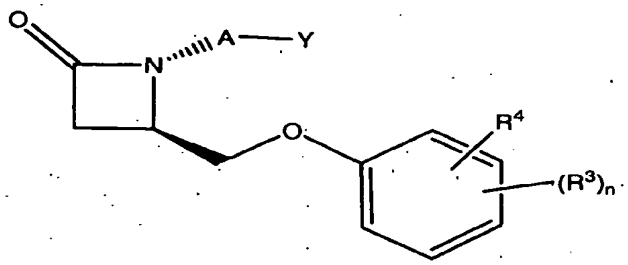
wherein R^3 is independently methyl, ethyl, isopropyl, fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, NH_2, OH, CN, NO_2, or CF_3; and
n is 0, 1, 2, or 3.

8. Use of claim 7, said compound comprising



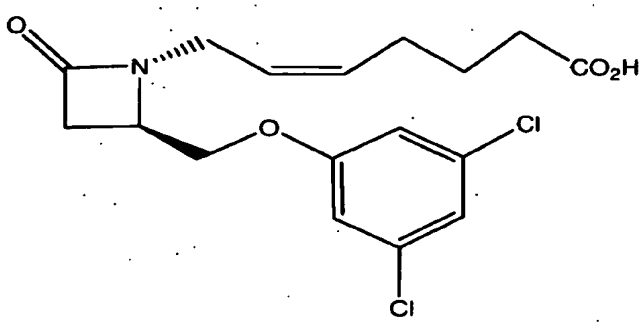
or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein a dashed line indicates the presence or absence of a covalent bond.

9. Use of claim 2, said compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein R^3 is independently methyl, ethyl, isopropyl, fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, NH_2, OH, CN, NO_2, or CF_3;
R^4 is hydroxyhydrocarbyl having from 1 to 10 carbon atoms; and
n is 0, 1, 2, or 3.

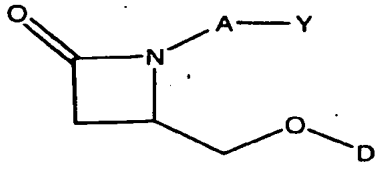
10. A compound comprising



or a pharmaceutically acceptable salt or a prodrug thereof.

ABSTRACT

Disclosed herein is a compound comprising



or a pharmaceutically acceptable salt or a prodrug or a metabolite thereof; wherein Y, A and D are described herein.

Methods, compositions, and medicaments related thereto are also disclosed.